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New opportunities for the synthesis of quinoxaline derivatives

Convenient methods for the synthesis of quinoxaline derivatives with the use of nucleophilic aromatic substitution of hydrogen in heteroaromatic part of molecule in conditions of the acid catalysis were elaborated. The reactions of substitution of fluorine with amines in aromatic ring of 6,7-difluoroquinoxaline with the formation of monofluoro derivatives were studied.

Keywords: quinoxalines; 6,7-difluoroquinoxalines; quinoxalin-2-ones; 6,7-difluoroquinoxalin-2-ones; nucleophiles.

Received: 21.01.2019. Accepted: 12.02.2019. Published: 29.03.2019.

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Introduction

Among derivatives of quinoxaline, compounds possessing various types of biological activities were found [1–4]. Thus, the Quinoxidine and the Dioxidine are used as antimicrobial agents [5]. A series of quinoxalines was patented as antitumor drugs [6]. Also, quinoxalines are known to be applied as effective electroluminescent materials, dyes [7], organic semiconductors [8], building-blocks in the synthesis of anionic receptors [9] and cavitands [10, 11]. The actuality of search for new methods for obtaining of functionalized quinoxalines is explained by the variety of useful properties of these compounds.

Usually derivatives of quinoxalines are synthesized either in condensation of corresponding *o*-phenylenediamines with 1,2-dicarbonyl compounds or in substitu-

tion of easily leaving groups in the quinoxaline nucleus [12].

Current review covers the recent data we have obtained on the solution of one of the fundamental problems of organic chemistry: C–C bonding of azines and nucleophiles using environmentally friendly experimental methods. Here, we consider reactions of quinoxalines with C-nucleophiles mediated by proton quaternary salt formation in conditions of acidic catalysis or by anions in activation of C-nucleophiles by bases. Using of acidic or basic catalysis for activation of these reactions are in better agreement with demands of 'green chemistry', because the catalysts are easily removed and recovered. Obviously, the substitution of hydrogen occurs as a result of oxidation of the initially

formed σ -adducts by atmospheric oxygen or by special oxidants. The reactions of hydrogen substitution by the methodology of the S_N^H -functionalization of C-H bonds are the most promising way for the preparation of derivatives, functionalized in heterocyclic moiety of quinoxaline [13].

To obtain derivatives of the aromatic ring of quinoxaline, halogen-containing quinoxaline derivatives are used as objects of investigation. Fluorine is the most promising atom in the reactions of nucleophilic substitution from the point of view of mobility. It is worth noting, that substitution of the halogen atom in 6,7-difluoroquinoxalines for N-nucleophiles leads to structural analogues of fluoroquinolone antibiotics [14].

Some examples of the synthesis of quinoxaline derivatives in a heterocyclic nucleus when quinoxaline interacts with nucleophiles are known. Quaternary salts of quinoxalines form σ -adducts in liquid ammonia [15]. Quinoxaline hydrochloride on heating with *N,N*-dimethylaniline

in the presence of sulfur affords the product of substitution of the hydrogen [16]. Thus melting of these reactants in the presence of three-fold excess of sulfur leads to 2-(*N,N*-dimethylaminophenyl) — quinoxaline-2-thione and 3-(*N,N*-dimethylaminophenyl) — quinoxaline-2-thione in 12% and 71% yield respectively. When the reaction is carried out in DMF at 140 °C under an inert gas, the product is 2,2-biquinoxaline. However, without sulfur no reaction in the same conditions is observed.

Quinoxalylketenes were prepared as a result of substitution of the hydrogen upon heating of quinoxaline-2-ones with methylketenes in the presence of dimethyl sulfate [17]. Similarly, interaction of quinoxaline-2-one with acetophenones in the presence of boron trifluoride leads to 3-(2-hydroxy-2-*R*-vinyl)quinoxalin-2-ones [18].

This work is continuation of studies [13] on using methodologies of aromatic nucleophilic substitution of hydrogen and fluorine to obtain biologically active compounds.

Results and discussion

1. Nucleophilic substitution of hydrogen in heterocyclic fragment of quinoxalines

Due to the high reactivity of quaternary *N*-alkyl quinoxaline salts, diaddition or cycloaddition products in the reactions with C-nucleophilic reagents are formed [19]. The synthesis of products of nucleophilic substitution of hydrogen atoms in the heterocyclic part of unsubstituted quinoxaline in the literature wasn't described earlier.

Recently, we succeeded in synthesizing various products of monosubstitution of quinoxaline under the conditions of acid catalysis. We have reported [20, 21] that quinoxalines (**1a,b**) interact with CH-acids

like dimedon, indanedione and 3-methyl-1-phenylpyrazol-5-one in DMSO at r.t. in the presence of an acid with formation of the products of monosubstitution of the hydrogen **2a,b-4a,b** (yields 36–50%). Dimers of quinoxaline **7a** were also obtained (yields 5–11%).

The reactions of compounds **1a** or **1b** with resorcinol in boiling ethanol in the presence of hydrochloric acid results in (quinoxalin-2-yl)benzene-1,3-dioles (**5a,b**) in yields 25–30%. Unsubstituted quinoxaline (**1a**) reacts with 1,3-dimethylbarbituric acid at room temperature with formation of a product of the hydrogen substitution **6a** without external acidic catalysis (yield 36%) [22] (Scheme 1).

Theoretically, the substitution of hydrogen in the heterocycle of quinoxalines with C-nucleophiles under acid catalysis in the presence of air oxygen is a simple, non-waste method for the preparation of monosubstituted quinoxaline derivatives with the formation of water as a result of the reaction. When the reaction is carried out in a solution of dimethyl sulfoxide and the addition of hydrochloric acid, the yield of the desired substitution products **2–6** does not exceed 35–40% due to the formation of side products — dimers of quinoxaline **7a,b**.

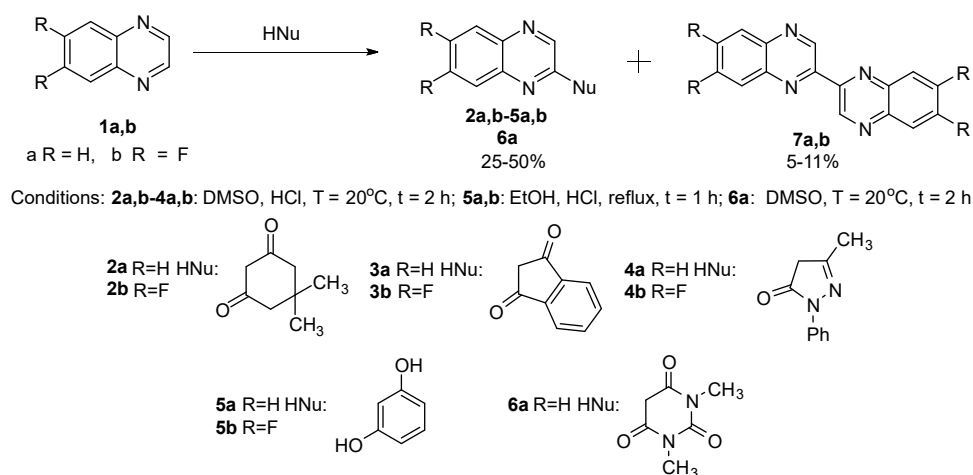
The EPR study of reaction mixture revealed formation of a stable dication radical **A** of starting quinoxaline [23]. It seems that formation of the products of monosubstitution **2a,b–4a,b** in the atmosphere of nitrogen (or in the lack of oxygen) is due to attack of nucleophile onto atom C² of quinoxaline followed by oxidation of the intermediated **B** and **C** with starting quinoxalines (**1a,b**) or protonated salts thereof. In their turn, intermediates **B** and **C** are oxidized thereby reducing the starting proton salts of quinoxaline into

the cation-radical **A**. Interaction of cation-radical **A** with starting quinoxalines (**1a,b**) is a typical example of hetarylation [24] with formation of dimers **7a,b** (Scheme 2).

When the reaction is carried out under a nitrogen atmosphere, the yield of substitution product is 25–40%, and the yield of quinoxaline dimer is 10–15%. Carrying out of reaction at bubbling of air the yield of target products can be increased to 45–55%.

Indole and derivatives thereof are widely used as heterocyclic C-nucleophiles in binding with various heterocyclic substrates [25]. The search for biologically active compounds among the indole derivatives is rather promising task since the indole ring acts as a constituent part of a series of important naturally occurring compounds like amino acids (tryptophan), neuromediator (serotonin) and antibiotic (Turbomycine A) [26].

In our work [27] we have established that upon heating in acetic acid, 6,7-difluoroquinoxaline (**1b**) reacts with methylin- doles **8a,b** with formation of correspond-



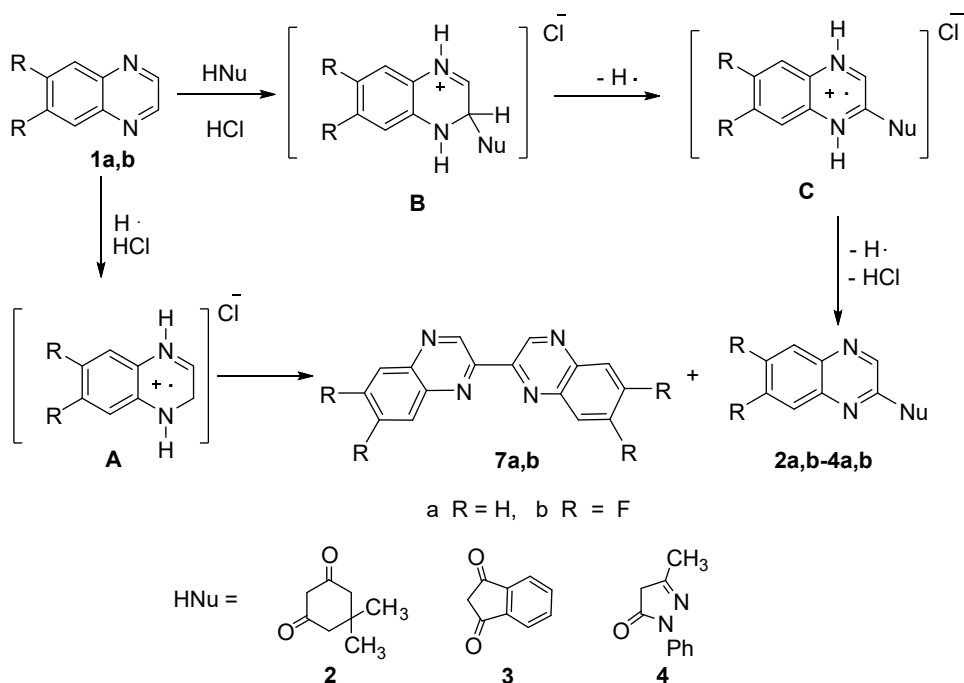
Scheme 1. Synthesis of 2-monosubstituted derivatives of quinoxalines in reactions with C-nucleophiles

ing products of substitution of hydrogen **9a,b** in yields 25–40% (Scheme 3).

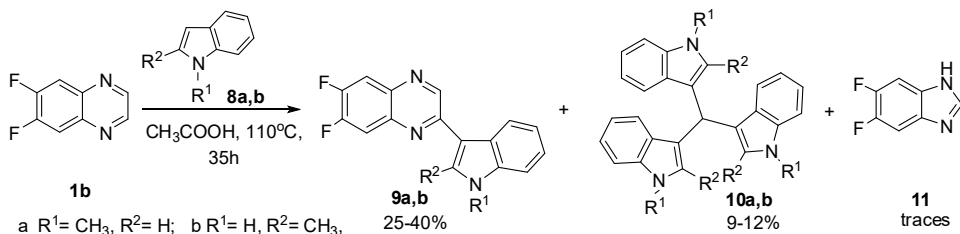
Interestingly, that along with the products **9a,b**, corresponding derivatives of tris(indol-3-yl)methane **10a,b** were isolated from the reaction mixtures. Additionally, 5,6-difluorobenzimidazole (**11**) was detected in the reaction mixture by means of TLC and mass-spectrometry.

Apparently, direct substitution of hydrogen in quinoxaline **1b** upon action of indoles is mediated by σ -adducts which are further oxidized spontaneously with the oxygen from the air.

The new quinoxaline transformation that we discovered is the result of a sequence of unit processes: competitive nucleophilic addition of the indole and the hydroxyl from water at the heterocyclic



Scheme 2. The proposed mechanism of interaction of quinoxalines with C-nucleophiles in conditions of acid catalysis



Scheme 3. Transformation of quinoxaline upon interaction with indoles

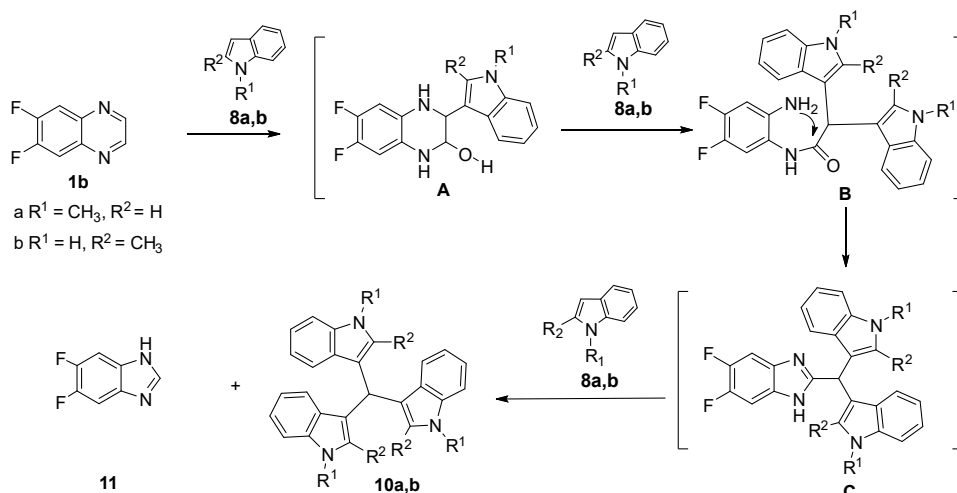
nuclei of quinoxaline (**A**); cleavage of one of C=N bonds; cyclization of **B** intermediate; substitution of the benzimidazole moiety in intermediate **C** (Scheme 4).

The discovered transformation of 6,7-difluoroquinoxalines in reactions with indoles lead to the synthesis of potentially biologically active compounds including derivatives of tris-indolylmethane homologs of Turbomycin A antibiotic [26].

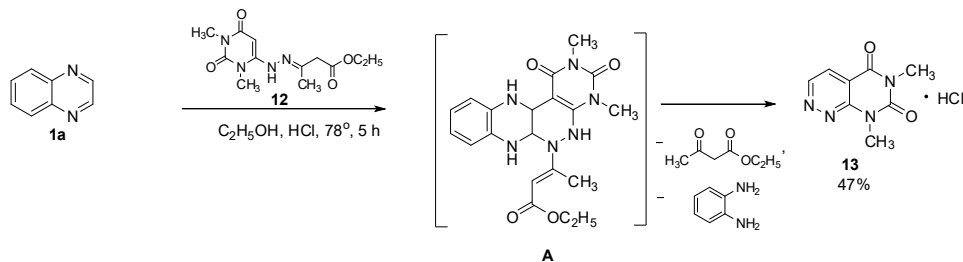
We have found [22] that quinoxaline (**1a**) reacts with ethyl 3-(2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazono)butanoate (**12**) upon heating in ethanol in the presence of hydrochloric acid converts into 6,8-dimethylpyrimido[4,5-c]pyridazine-

5,7(6*H*,8*H*) — dione hydrochloride (**13***HCl), yield 47%. Being treated in suspension with aqueous ammonia, it gives free base **13** which has mp and spectral data identical to the same compound described in [28] (Scheme 5).

The mechanism for formation of pyridazinepyrimidine **13** probably comprises the two steps: 1) nucleophilic addition of the hydrazone of 1,3-dimethyl-6-hyrazinouracile (**12**) in a role of 1,4-dinucleophile to C²-C³ bond in quinoxaline with generation of intermediate **A**; 2) aromatization of pyridazine ring with formation of the final product. In overall process, quinoxaline (**1a**) acts as a donor of two-carbon fragment.



Scheme 4. The proposed mechanism for the formation of tris-indolylmethanes in the reaction of quinoxalines with indoles



Scheme 5. The mechanism of formation of the pyridazinopyrimidine **13**

2. Reaction of quinoxalines with 3-methyl-1-phenylpyrazol-5-one in the basic conditions

In basic conditions, quinoxalines **1a,b** react with 3-methyl-1-phenylpyrazol-5-one (**4**) in a different way than in the presence of acid. When triethylamine was used as a base, we obtained tetrapyrazolyethane **14** (yield 47–51%) and the dipyrazolylmethane **15** (yield 7–9%) [29] (Scheme 6).

It is worth to note that upon short boiling in DMF tetrapyrazolyl derivative **14** converts into dipyrazolylmethane **15**. The same process is observed in DMF at r.t. in the presence of iodine and upon heating of the crystals of compound **14** up to 255–260 °C (Scheme 6).

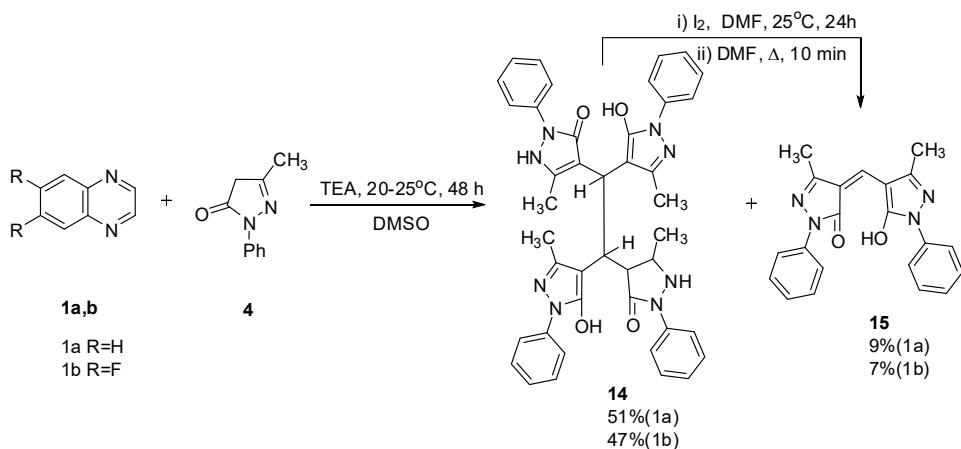
Plausible mechanism for formation of tetrapyrazolyethane **14** from quinoxalines **1a,b** consist in the two following steps: nucleophilic addition of two molecules of pyrazolone **4** onto C=N bonds in quinoxalines **1a,b** with formation of bis-adduct **A**; cleavage of the adduct **A** with formation of intermediate **B** which further transforms into tetrapyrazolyethane **14** (Scheme 7).

Remarkably that compounds **14** and **15** were prepared in combination with 3-methyl-1-phenylpyrazol-5-one (**4**) both from unsubstituted **1a** and 6,7-difluoroquinoxaline (**1b**) in similar conditions. This is an evidence of that the fluorine substituents don't affect the reaction substantially.

3. Reactions of quinoxalin-2-ones with C-nucleophiles

As it was mentioned above, unsubstituted quinoxaline is unstable and prone to transformations with decomposition of the heterocyclic ring upon interaction with C-nucleophiles. Consequently, functionalization of C-H bond may be accompanied with side destructive processes, which diminish the yield of desired quinoxaline derivatives. In this aspect, more stable quinoxalin-2-one derivatives are more promising building-blocks.

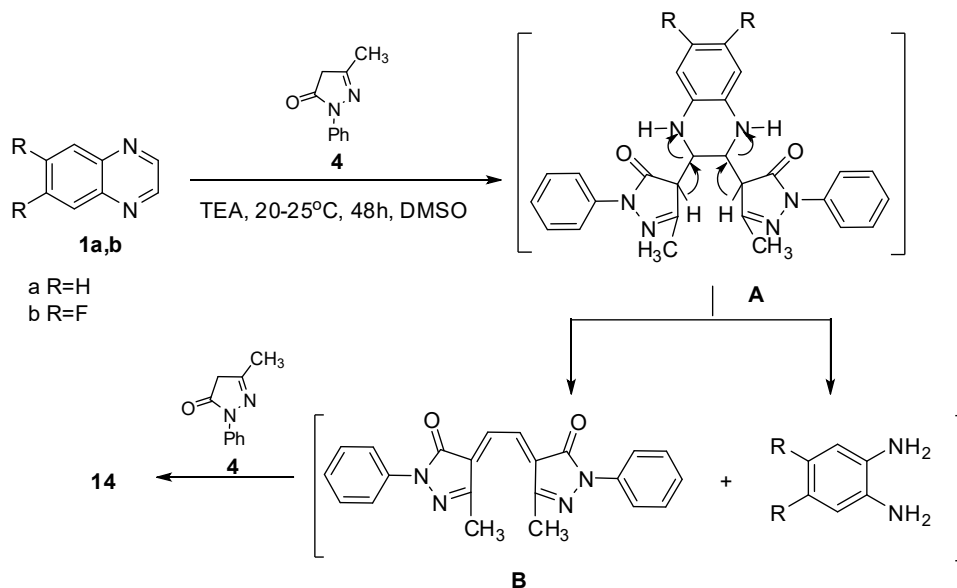
The synthesis of (2-oxo-1,2-dihydroquinoxalin-3-yl)methyl ketones in reaction of quinoxalin-2-one with ketones in dimethyl sulfate is described earlier [17]. 3-Indolyl derivative of quinoxalin-2-one was prepared from its reaction with indole in the presence of acylating reagents [30].



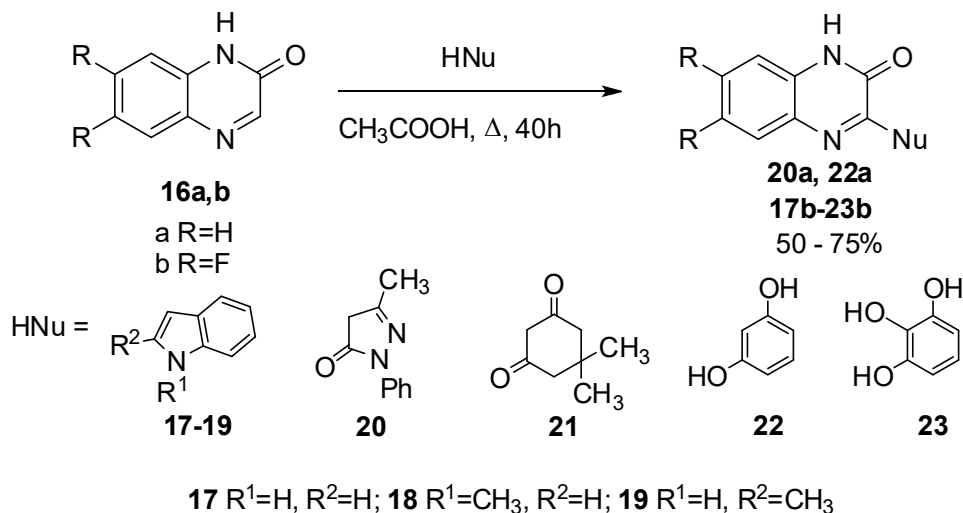
Scheme 6. The reaction of quinoxalines **1a,b** with 3-methyl-1-phenylpyrazol-5-one (**4**)

We have established that in contrast to quinoxalines (**1a,b**) (see Scheme 1), interaction of quinoxaline-2-ones (**16a,b**) with nucleophiles in DMSO solution at room temperature in the presence of an acid does not cause nucleophilic substitu-

tion of the hydrogen. Compounds **16a,b** upon heating with C-nucleophiles in acetic acid give the products of substitution of the hydrogen in heterocyclic ring **20a, 22a, 17b-23b** in yields 50–75% (Scheme 8) [31].



Scheme 7. The proposed mechanism for the formation of tetrapyrazolyethane **14** in the reaction of quinoxalines with 3-methyl-1-phenylpyrazol-5-one (**4**)

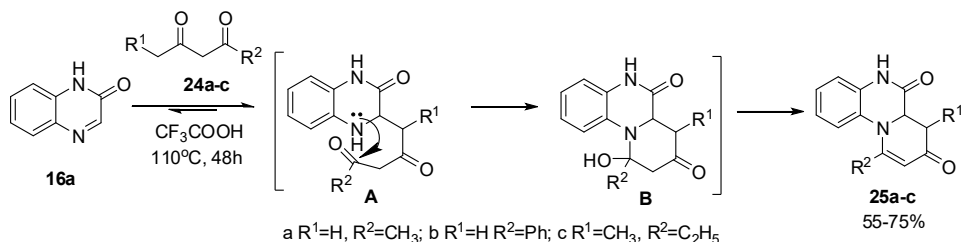


Scheme 8. Synthesis of 3-monosubstituted quinoxaline-2-ones in reactions with C-nucleophiles

The above described examples of direct substitution of the hydrogen in the series of quinoxaline-2-one derivatives present simple and eco-friendly method for the preparation of the products of C–C bonding which does not require additional oxidizers since intermediate σ -adducts are spontaneously oxidized with the oxygen from the air during the reaction.

With the aim of elaboration of effective methods for functionalization of quinoxaline-2-one (**16a**), we have studied its transformation with β -diketones in the conditions of acid catalysis. Thus in the paper [32], we have reported that quinoxaline-2-one (**16a**) reacts with acetylacetone (**24a**), benzoyl acetone (**24b**) and heptan-3,5-dione (**24c**) upon heating in TFA affording the derivatives of 6a,7-dihydropyrido[1,2-a]quinoxaline-6,8-dione (**25a-c**) (yields 55–75%) (Scheme 9).

The formation of tricyclic system of pyridoquinoxalinediones **25a-c** could be explained as a sequence of the following stages: an attack of α -atom of carbon in terminal alkyl from β -diketone onto C=N bond from quinoxaline-2-one (**16a**); intramolecular addition-cyclization onto C=O group in the intermediate **A** with its transformation in intermediate **B**; dehydration of **B** intermediate with formation of the final tricyclic products **25a-c**.



Scheme 9. Synthesis of 6a,7-dihydropyrido[1,2-a]quinoxaline-6,8-dione derivatives by the interaction of quinoxalin-2-one with β -diketones

In our investigation, it was found [33] that quinoxaline-2-one (**16a**) reacts in acidic conditions with aliphatic aldehydes **26a-c** to give derivatives of pyrido[1,2-a]quinoxalinium **27a-c**, yields 35–55% (Scheme 10). Similarly quinoxaline-2-one (**16a**) reacts with 3-phenylpropanal (**26d**) and phenylacetaldehyde (**26e**). Individual derivatives of pyrido[1,2-a]quinoxalinium **27d,e** were isolated only as picric salts **28d,e**. The picrate **28a** was synthesized specially to perform structural comparison of zwitter-ion from corresponding picrate.

4. Nucleophilic substitution of fluorine in aromatic fragment of quinoxaline and quinoxalin-2-one

The presence of two fluorine atoms in a molecule of 6,7-difluoroquinoxaline open new possibilities for modifications upon its aromatic cycle. A series of examples of the synthesis of quinoxaline derivatives by substitution of the fluorine atoms with N-nucleophiles was described earlier [34].

In the paper [20] we have reported that compounds **2b-4b** react smoothly with *N*-methylpiperazine in DMF solution at 115–120 °C with formation of corresponding derivatives of quinoxaline **29-31** in 53–61% yield (Scheme 11).

Monofluoro compounds **29-31** are the main products of substitution of fluorine in reaction of difluoroquinoxalines **2b-4b** with *N*-methylpiperazine which implies

that the substituent in their position 2 activates rather the F⁷ atom than F⁶ one to nucleophilic substitution.

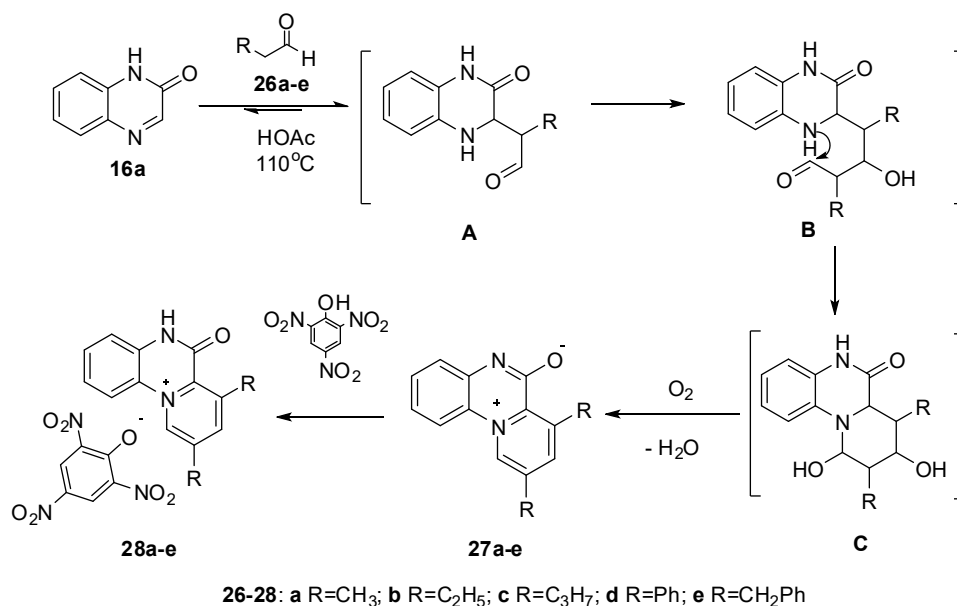
We have experimentally established [31] that 6,7-dufluoroquinoxalin-2-ones

17b-19b react with *N*-methylpiperazin in DMSO solution at 145–150 °C with formation of corresponding 7-(*N*-methylpiperazin) — substituted quinoxalin-2-ones **32-34** in 55–69% yield (Scheme 12).

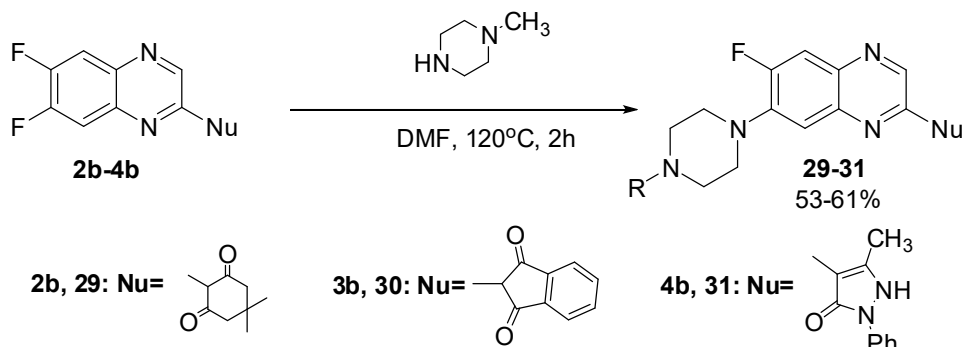
Conclusion

In the current review, we combined our latest results on the development of convenient methods for implementation of S_N^H methodology of functionalization of C–H bonds for preparation of the quinoxaline

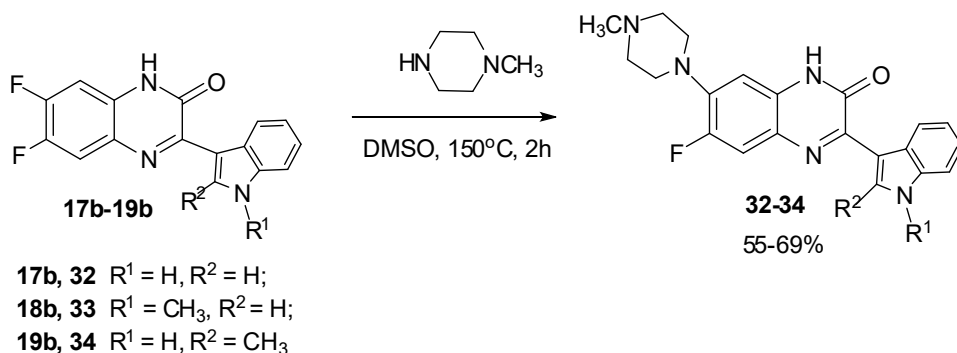
derivatives. As a result of the reactions of quinoxalines with C-nucleophiles under acid catalysis conditions, new hydrogen substitution products in the heteronuclear core were obtained. It should be noted that



Scheme 10. The interaction of quinoxalin-2-one with aldehydes



Scheme 11. Synthesis of 6-alkylamino-7-fluoro derivatives of quinoxaline



Scheme 12. Synthesis of 6-fluoro-7-alkylamino derivatives from 3-substituted 6,7-difluoroquinoxalin-2-ones

the substitution of hydrogen occurs as a result of the addition of nucleophiles and the spontaneous oxidation of adducts under the action of atmospheric oxygen without the use of special oxidizers and expensive

catalysts. Under conditions of basic catalysis, the products of selective substitution of fluorine atoms with N-nucleophiles in the aromatic nucleus of 6,7-quinoxalines were synthesized.

Acknowledgements

The research was supported by the Russian Foundation for Basic Research (grant: 18-33-00727 mol_a, grant: 18-03-00715 A) and the Russian Science Foundation (project 18-13-00161).

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